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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,144	07/16/2001	Nassar Chegini	G0651/7026	6136

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,144	CHEGINI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/3/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/03/03 has been entered.

2. Claims 1, 11-14 are pending and under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Actions, mailed 1/13/03 and 7/29/03.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

At issue is whether or not the claimed TIMP-1 antibodies or Fab fragments thereof would function in prevention or remediation of "surgical adhesions". The specification assessed whether MMP and TIMP expression is altered in patients who do or do not have adhesion. The specification on page 6, lines 19-23, discloses that an unbalanced level of MMP-1 and TIMP-1, high TIMP-1 expression, and association of a major portion of MMP-1 in complex with TIMP-1 may b major contributing factors in the peritoneal environment which provide a favorable condition leading to adhesion development. The exemplification is drawn to comparative study by examining the expression of MMP-1, TIMP-1 and MMP-1/TIMP-1 complex in various intraperitoneal tissues including pariental peritoneum, uterus, fallopian tube, ovary, bowel, omentum and adhesions as well as in skin, fascia, and peritoneal fluids in patients who were under going abdominal/pelvic surgical procedures (paged 7-8).

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animals were used as model system for the prevention or remediation of surgical adhesions. It is not clear that reliance on a comparative study of the expression of MMP-1, TIMP-1 and MMP-1/TIMP-1 complex data in various intraperitoneal tissues accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively prevent surgical adhesions or reach any therapeutic endpoint in human by administrating the therapeutic composition. The specification does not teach how to extrapolate data obtained from the comparative study studies to the development of effective in vivo human therapeutic prevention, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic formulation comprising TIMP-1 antibodies exemplified in the specification.

However, an effective protocol for the prevention or remediation of surgical adhesions in human is subject to a number of factors which enter the picture beyond simply the administration of the therapeutic formulation in an acceptable formulation. Demonstrating unbalanced level of MMP-1, and TIMP-1, High TIMP-1 expression and association of a major portion of MMP-1 in complex with TIMP-1 cannot alone support the predictability of the method for prevention or remediation of surgical adhesions through administration of the appropriate formulation. The ability of a host to suppress and thereby prevent surgical adhesions will vary depending upon factors such as the condition of the host.

The specification does not provide sufficient teaching as to how it can be assessed that prevention or remediation of surgical adhesions in the comparative studies was achieved after the administration of the therapeutic composition of the invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 12/3/03, have been fully considered, but have not been found convincing.

Applicant asserts that the experimental data disclosed in the application suggests that adhesions exist in a molecular environment that prevents proteolytic degradation by matrix metalloproteinases (MMPs), and TIMP-1 may have a stimulatory effect on cell growth, including fibroblasts which migrate into the site of injury at the initial stage of adhesion formation. Applicant submits that the correlation between TIMP-1 and the occurrence of surgical adhesions establishes by the experimental data, the method for prevention or remediation of surgical adhesions by administering a therapeutic formulation containing anti-TIMP-1 antibodies to a patient was developed. Applicant contends that the teaching within the specification concerning

the manner of making and using the subject invention must be taken as true unless the Patent Office can cite specific reasons to doubt the objective truth of the statements contained therein.

Again, the specification fails to provide *in vitro* or *in vivo* exemplification that is drawn to the efficacy of the claimed antibodies for the prevention or remediation of surgical adhesions. While a correlation between the levels of TIMP-1 in the peritoneal cavity and the tendency of the patients to develop adhesions may provide an indication that particular compounds/compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention. The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-prevention or remediation of surgical adhesions- and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying adhesion molecule and physiologic bases of the therapeutic effects of anti-TIMP-1 in the prevention or remediation of surgical adhesions.

Applicant submits that it is well settled in patent law that the standard is whether undue experimentation would be required by one of ordinary skill in the art in order to practice the claimed invention, given the benefit of the subject application rather than the amount of guidance and direction required is high to enable a person of ordinary skill in the art to practice the present invention as stated in previous Office Action.

The Examiner agree with the Applicant assertion to the extent of the standard is whether undue experimentation would be required by one of ordinary skill in the art in order to practice the claimed invention. However, to determine whether a disclosure would require undue experimentation, the Examiner relies on the "Wands Factors" from *In re* Wands. Based on the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

Applicant submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. Applicant asserts that the Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. Scott v. Finney, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Applicant concludes that given the state of the art, as demonstrated by the scientific publications submitted herewith, one of ordinary skill in the art can readily determine appropriate dosages, routes of administration, etc, without resort to undue experimentation. Thus, the applicants respectfully submit that the subject specification enables the claimed antibody-mediated treatment methods.

However, the specification must disclose enabling invention that is useful, and that is disclosed adequately to enable its use.

Applicant draws the Examiner's attention to the following articles:

1. Rothlein R. et a1., "Treatment of Inflammation with .Anti-lCAM-1", Res. Immunol., 1993, 144(9):735-739,

2. Wegner C. et al., "Efficacy of Monoclonal Antibodies Against Adhesion Molecules in Animal Models of Astbma", Agents Actions Suppl., 1993, 43:151-162;

3. Zhang R. et a1., "Anti-ICAM-l Antibody Reduces Ischemic Cell Damage After Transient Middle Cerebral Artery Occlusion in the Rat", Neurology, 1994, 444(9):1747-17519,

4. Maguire H. et al., "Neutralizing Anti-IL-10 Antibody Upregulates the Induction and Elicitation of Contact Hypersensitivit", J Interferon Cytokine Res, 1997, 17412):763-768;

5. Iimuro Y. et al., "Arltibodies to Tumor Necrosis Factor Alpha Attenuate hepatic Necrosis and Inflammation Caused by Chronic Exposure to Ethanol in the Rat", Hepatology, 1997, 6(6):1530-15374,

6. Walter U. et al., "Generation and Characterization of a Novel Adhesion Function Blocking Monoclonal antibody Recognizing Both Rat and Mouse E selectin", Hybridoma, 1997, 16(4):355-361,

7. Petit A. et al., "Neutralizing Antibodies Against Epidermal Growth Factor and ErbB-2/neu Receptor Tyrosine Kinases Down-Regulate Vascular Endothelial Growth Factor Production by Tumor Cells In Vitro and In Vivo", Am. J Pathol., 1997, 15146):1523-1530;

8. Van Deventer S. and Comoglio L., "Monoclonal Antibody Therapy of Inflammatory Bowel Disease", Pharm. World Sci., 1997, 19(2):55-59;

9. Lorenz H. et a1.,"In vivo Blockade of TNF-α by Intravenous Infusion of a Chimeric Monoclonal TNF-α Antibody in Patients with Rheumatoid Arthritis", J Immunol., 1996, 156(4):1646-1653;

10. Henricks P. and Nijkamp F., "Pharmacological Modulation of Cell Adhesion Molecules", Eur. J Pharmacol., 1998, 344(1):1-13,.

11. Yamasaki Y. et al., 'New Therapeutic Possibility of Blocking Cytokine-Induced Neutrophil Chemoattractant on Transient Ischemic Brain Damage in Rats", Brain Res, 1997, 759(1):103-111.

12. U.S. Patent No. 5,744,442,

13. Forough et al., "Generating Antibodies Against Secreted Proteins Using Vascular Smooth Muscle Cells Transduced with Replication-Defective Retrovirus", Bio Techniques 20:694-701, 1996),

14. Khokha et al. "Antisense RNA-Induced Reduction in Murine TNP Levels Confers Oncogenicity on Swiss 313 Ce11s", Science, New Series, 24344893):947-950, 1989; and

15. Alexander, C. et al. "Targeted Disruption of the Tissue Inhibitor of Metalloproteinases Gene Increases the Invasive Behavior of Primitive Mesenchymal Cells Derived from Embryonic Stem Cells In Vitro" J Cell Biology 118(3):727-739, 1992).

Again, these articles do provide some support that antibodies may be used in therapeutic treatment purposes in certain situations. However, none of these references used TIMP-1 antibodies *in vivo* or prevent surgical adhesions. Thus it is unclear how administering anti-TIMP-1 in vivo would prevent surgical adhesions. Further, while the anti-TIMP-1 antibodies are available, however the method of using the anti-TIMP-1 in vivo for prevention or remediation of surgical adhesions is not disclose. Therefore, these articles/patent do not address the point at issue.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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